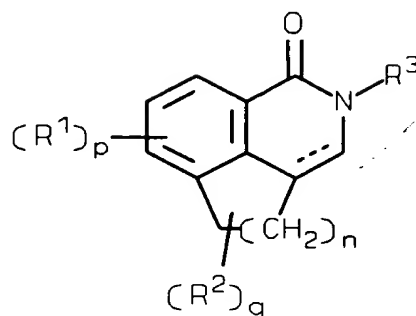


CM  
—  
5

WE CLAIM:

1. A compound of Formula I



PS  
PI  
L

in which

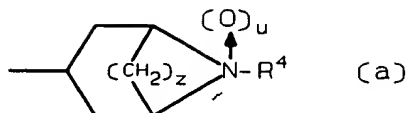
- 15 the dashed line denotes an optional double bond;  
 n is 1, 2 or 3;  
 p is 0, 1, 2 or 3;  
 q is 0, 1 or 2;  
 each R¹ is independently selected from halogen, hydroxy,  
 20 lower alkoxy, lower alkyl, nitro, amino, amino carbonyl,  
 (lower alkyl)amino, di(lower alkyl)amino, and  
 (lower alkanoyl)amino;  
 each R² is lower alkyl; and
- PI

69

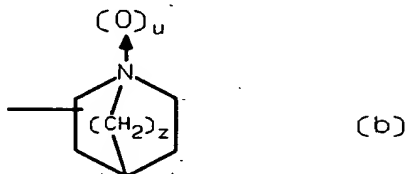
P1

$R^3$  is a group selected from Formulae (a), (b), (c) and (d):

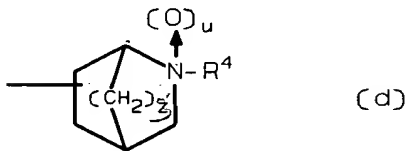
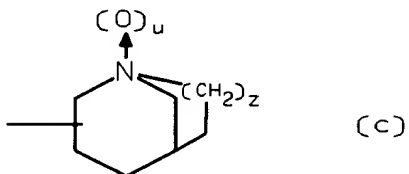
5



10



15



in which

20  $u$  is 0 or 1;

$z$  is 1, 2 or 3; and

$R^4$  is  $C_{1-7}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl- $C_{1-2}$  alkyl, or a group  $(CH_2)_t R^5$  where  $t$  is 1 or 2 and  $R^5$  is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from  $C_{1-4}$  alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and  $C_{1-4}$  alkyl optionally substituted by hydroxy,  $C_{1-4}$  alkoxy, carboxy, esterified carboxy or *in vivo* hydrolyzable acyloxy; the pharmaceutically acceptable salts, individual isomers, or mixtures of isomers thereof.

35

H 2. A compound of Claim 1 in which both q and u are 0, p is 0, 1 or 2, each R<sup>1</sup> is independently selected from halogen, lower alkoxy or amino and R<sup>4</sup> is lower alkyl.

5

H 3. A compound of Claim 2 in which p is 0, and R<sup>4</sup> is methyl.

P1 4. A compound of Claim 3 in which R<sup>3</sup> is one of the following groups:

15 1-azabicyclo[2.2.2]oct-3-yl;  
1-azabicyclo-[2.2.2]oct-4-yl;  
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
15 endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
endo-1-azabicyclo[3.3.1]non-4-yl; or  
exo-1-azabicyclo[3.3.1]non-4-yl.

20

5. A compound of Claim 4 in which the optional bond is present.

6. A compound of Claim 5 in which n is 1.

H 25

7. A compound of Claim 6 in which R<sup>3</sup> is 1-azabicyclo[2.2.2]oct-3-yl, namely 2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopent[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

30

8. A compound of Claim 7 which is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetrahydrocyclopenta[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

35

9. A compound of Claim 8 which is  
(S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5-tetra-  
hydrocyclopenta[de]isoquinolin-1-one hydrochloride.

H 5 10. A compound of Claim 6 in which R<sup>3</sup> is  
8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely,  
2-(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-  
1,2,4,5-tetrahydro-cyclopent[de]isoquinolin-1-one or a  
pharmaceutically acceptable salt thereof.

10 11. A compound of Claim 10 which is  
2-(endo-8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-  
1,2,4,5-tetrahydro-cyclopent[de]isoquinolin-1-one or a  
pharmaceutically acceptable salt thereof.

15 12. A compound of Claim 11 which is  
2-(endo-8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-  
1,2,4,5-tetrahydro-cyclopent[de]isoquinolin-1-one  
hydrochloride.

20 13. A compound of Claim 5 in which n is 2.

H 14. A compound of Claim 13 in which R<sup>3</sup> is  
1-azabicyclo[2.2.2]oct-3-yl, namely  
25 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-  
1H-benz[de]isoquinolin-1-one or a pharmaceutically  
acceptable salt thereof.

15. A compound of Claim 14 which is  
30 (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetra-  
hydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically  
acceptable salt thereof.

16. A compound of Claim 15 which is  
35 (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetra-  
hydro-1H-benz[de]isoquinolin-1-one hydrochloride.

72

17. A compound of Claim 14 which is  
(R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetra-  
hydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically  
acceptable salt thereof.

5

18. A compound of Claim 17 which is  
(R)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetra-  
hydro-1H-benz[de]isoquinolin-1-one or hydrochloride.

H 10

19. A compound of Claim 13 in which R<sup>3</sup> is  
1-azabicyclo[2.2.2]oct-4-yl, namely  
2-(1-azabicyclo[2.2.2]oct-4-yl)-2,4,5,6-tetrahydro-  
1H-benz[de]isoquinolin-1-one or a pharmaceutically  
acceptable salt thereof.

15

H

20. A compound of Claim 13 in which R<sup>3</sup> is  
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl, namely  
2-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-  
2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one.

20

H

21. A compound of Claim 13 in which R<sup>3</sup> is  
8-methyl-8-azabicyclo[3.2.1]oct-3-yl, namely  
2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-  
2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a  
pharmaceutically acceptable salt thereof.

25

22. A compound of Claim 21 which is  
2-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-  
2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a  
pharmaceutically acceptable salt thereof.

30

23. A compound of Claim 21 which is  
2-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-  
2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a  
pharmaceutically acceptable salt thereof.

35

73

H

24. A compound of Claim 13 in which R<sup>3</sup> is  
*endo*-1-azabicyclo[3.3.1]non-4-yl, namely  
 2-(*endo*-1-azabicyclo[3.3.1]non-4-yl)-2,3,5,6-tetra-  
 hydro-1*H*-benz[*de*]isoquinolin-1-one or a pharmaceutically  
 5 acceptable salt thereof.

25. A compound of Claim 5 in which n is 3.

H

26. The compound of Claim 25 in which R<sup>3</sup> is  
 10 1-azabicyclo[2.2.2]oct-3-yl, namely  
 2-(1-azabicyclo[2.2.2]oct-3-yl)-1,2,4,5,6,7-hexahydro-  
 cyclohept[*de*]isoquinolin-1-one or a pharmaceutically  
 acceptable salt thereof.

15 27. A compound of Claim 4 in which the optional  
 bond is absent.

28. A compound of Claim 27 in which n is 1.

20 29. A compound of Claim 27 in which n is 2.

H

30. A compound of Claim 29 in which R<sup>3</sup> is  
 1-azabicyclo[2.2.2]oct-3-yl, namely  
 2-(1-azabicyclo-[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexa-  
 25 hydro-1*H*-benz[*de*]isoquinolin-1-one.

31. A compound of Claim 30 which is  
 2-(1-azabicyclo-[2.2.2]oct-3*S*-yl)-  
 2,3,3a*S*,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one or  
 30 a pharmaceutically acceptable salt thereof.

32. A compound of Claim 31 which is  
 2-(1-azabicyclo-[2.2.2]oct-3*S*-yl)-  
 2,3,3a*S*,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one  
 35 hydrochloride.

74

33. A compound of Claim 30 which is  
2-(1-azabicyclo-[2.2.2]oct-3S-yl)-  
2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one or  
a pharmaceutically acceptable salt thereof.

5

34. A compound of Claim 33 which is  
2-(1-azabicyclo-[2.2.2]oct-3S-yl)-  
2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one  
hydrochloride.

10

35. A compound of Claim 30 which is  
2-(1-azabicyclo-[2.2.2]oct-3R-yl)-  
2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one or  
a pharmaceutically acceptable salt thereof.

15

36. A compound of Claim 35 which is  
2-(1-azabicyclo-[2.2.2]oct-3R-yl)-  
2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one  
hydrochloride.

20

37. A compound of Claim 30 which is  
2-(1-azabicyclo-[2.2.2]oct-3R-yl)-  
2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one or  
a pharmaceutically acceptable salt thereof.

25

38. A compound of Claim 37 which is  
2-(1-azabicyclo-[2.2.2]oct-3R-yl)-  
2,3,3aR,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one  
hydrochloride.

30

39. A compound of Claim 27 in which n is 3.

35 Claim 4 in combination with a pharmaceutically  
acceptable excipient.

41. A method for treating a condition chosen from emesis, a gastro-intestinal disorder, CNS disorder, a cardiovascular disorder and pain in an animal in need of such treatment, which method comprises administering a therapeutically effective amount of a compound of Claim 1 to such animal.

42. A method of Claim 41 in which the condition is a gastrointestinal disorder.

43. A method of Claim 41 in which the condition is a cardiovascular disorder.

44. A method of Claim 41 in which the condition is pain.

45. A method of Claim 41 in which the condition is a CNS disorder.

46. A method of Claim 41 in which the condition is anxiety/depressive state or anxiety/depression behavior.

47. A method of Claim 41 in which the condition is the side effects caused by withdrawal from an addictive substance.

48. A method of Claim 41 in which the condition is emesis.

49. A method of Claim 41 in which the condition is emesis in humans undergoing cancer treatment with a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis, or recovering from surgical anesthesia, or undergoing drug therapy in general in which a significant side effect is emesis.

35



<sup>48</sup>  
~~50~~. A method of Claim <sup>47</sup>~~49~~ in which the compound is (S)-2-(1-azabicyclo[2.2.2]oct-3-yl)-2,4,5,6-tetrahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

5

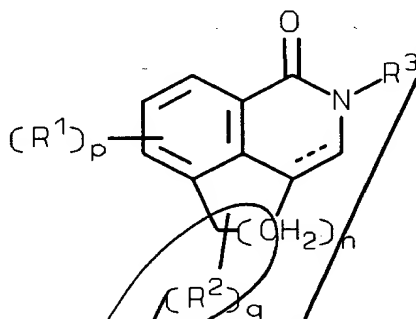
<sup>49</sup>  
~~51~~. A method of Claim <sup>47</sup>~~49~~ in which the compound is 2-(3S-1-azabicyclo-[2.2.2]oct-3-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one or a pharmaceutically acceptable salt thereof.

10

*Sub*  
~~52~~. A method for treating an animal having a condition in which the 5-HT<sub>2</sub> receptor plays a role, which method comprises administering a therapeutically effective amount of a compound of Claim 1 to such animal.

15

~~53~~. A process for the preparation of a compound of Formula I:



25

in which

~~30~~ the dashed line denotes an optional double bond;

n is 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 0, 1 or 2;

each R<sup>1</sup> is independently selected from halogen, hydroxy,  
~~35~~ lower alkoxy, lower alkyl, nitro, amino, amino carbonyl,  
 (lower alkyl)amino, di(lower alkyl)amino, and  
 (lower alkanoyl)amino;

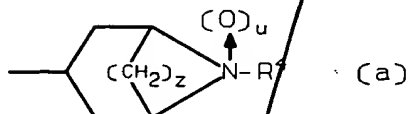
*claim 50*

*79*

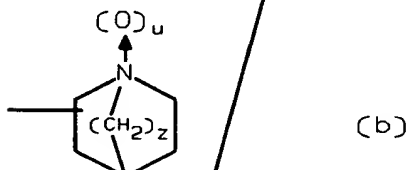
each  $R^2$  is lower alkyl; and  
 $R^3$  is a group selected from Formulae (a), (b), (c) and  
 (d):

26890c2

5



10



15



20

in which

$u$  is 0 or 1;

$z$  is 1, 2 or 3; and

$R^4$  is  $C_{1-7}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl- $C_{1-2}$  alkyl,  
 or a group  $(CH_2)_t R^5$  where  $t$  is 1 or 2 and  $R^5$  is thienyl,

25 pyrrolyl, or furyl, each optionally further substituted  
 by one or two substituents selected from  $C_{1-6}$  alkyl,  $C_{1-6}$

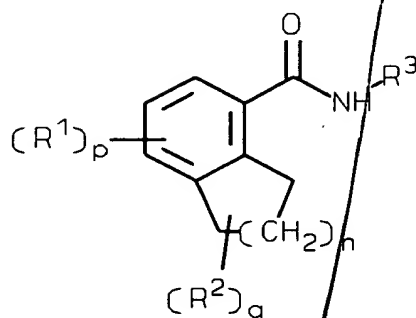
alkoxy, trifluoromethyl or halogen, or is phenyl  
 optionally substituted by one or two substituents  
 selected from  $C_{1-4}$  alkoxy, trifluoromethyl, halogen,

30

nitro, carboxy, esterified carboxy, and  $C_{1-4}$  alkyl  
 optionally substituted by hydroxy,  $C_{1-4}$  alkoxy, carboxy,  
 esterified carboxy or *in vivo* hydrolyzable acyloxy; the  
 pharmaceutically acceptable salts, individual isomers,  
 or mixtures of isomers thereof, which process comprises

35

(1) reacting a compound Formula II:



in which  $n$ ,  $p$ ,  $q$ ,  $R^1$ ,  $R^2$ , and  $R^3$  are as defined above with a formylating agent in the presence of a strong base and then acidifying to form a compound of Formula I in which the optional bond is present;

(2) optionally hydrogenating a compound of Formula I in which the optional bond is present to form a compound of Formula I in which the optional bond is absent;

(3) optionally reacting with or exchanging substituents present on a compound of Formula I to form an additional substituted compound of Formula I;

(4) optionally converting a salt of a compound of Formula I to a corresponding compound of Formula I;

(5) optionally converting a compound of Formula I to a corresponding pharmaceutically acceptable salt;

(6) optionally oxidizing a compound of Formula I in which  $u$  is 0 to the corresponding  $N$ -oxide;

(7) optionally reducing the  $N$ -oxide of a compound of Formula I to the corresponding compound of Formula I wherein  $p$  is 0; or

(8) optionally separating a mixture of isomers of a compound of Formula I into a single isomer.

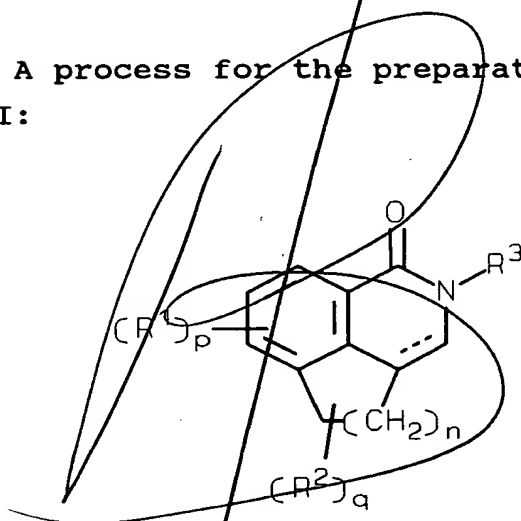
54. A process according to Claim 53 in which  $R^3$  is one of the following groups:

- 1-azabicyclo[2.2.2]oct-3-yl;  
 1-azabicyclo-[2.2.2]oct-4-yl;  
 5    *endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
      *exo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
      *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
      *exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
      *endo*-1-azabicyclo[3.3.1]non-4-yl; or  
 10    *exo*-1-azabicyclo[3.3.1]non-4-yl.

55. A process for the preparation of a compound of Formula I:

15

20



in which

25 the dashed line denotes an optional double bond;

$n$  is 1, 2 or 3;

$p$  is 0, 1, 2 or 3;

$q$  is 0, 1 or 2;

each  $R^1$  is independently selected from halogen, hydroxy,

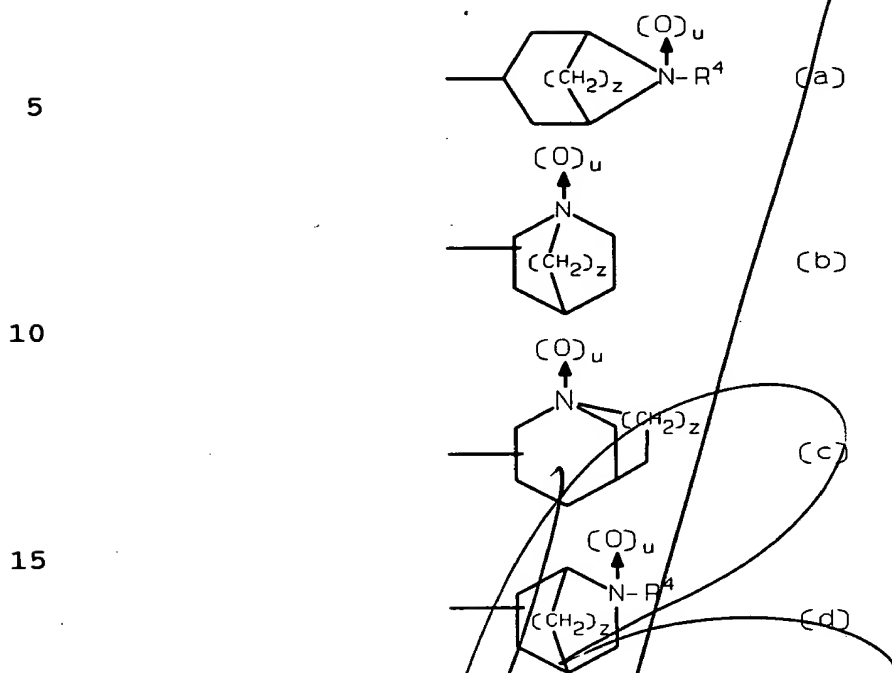
30 lower alkoxy, lower alkyl, nitro, amino, amino carbonyl,

(lower alkyl)amino, di(lower alkyl)amino, and

(lower alkanoyl)amino;

each  $R^2$  is lower alkyl; and

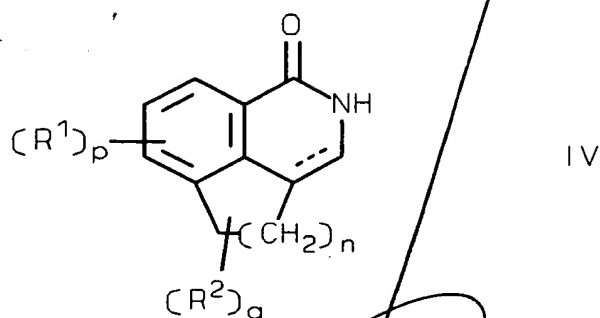
$R^3$  is a group selected from Formulae (a), (b), (c) and (d):



in which

20  $u$  is 0 or 1;  
 $z$  is 1, 2 or 3; and  
 $R^4$  is  $C_{1-7}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl- $C_{1-2}$  alkyl,  
or a group  $(CH_2)_t R^5$  where  $t$  is 1 or 2 and  $R^5$  is thienyl,  
pyrrolyl, or furyl, each optionally further substituted  
25 by one or two substituents selected from  $C_{1-6}$  alkyl,  $C_{1-6}$   
alkoxy, trifluoromethyl or halogen, or is phenyl  
optionally substituted by one or two substituents  
selected from  $C_{1-4}$  alkoxy, trifluoromethyl, halogen,  
nitro, carboxy, esterified carboxy, and  $C_{1-4}$  alkyl  
30 optionally substituted by hydroxy,  $C_{1-4}$  alkoxy, carboxy,  
esterified carboxy or in vivo hydrolyzable acyloxy; the  
pharmaceutically acceptable salts, individual isomers,  
or mixtures of isomers thereof, which process comprises

(1) reacting a compound of Formula IV:



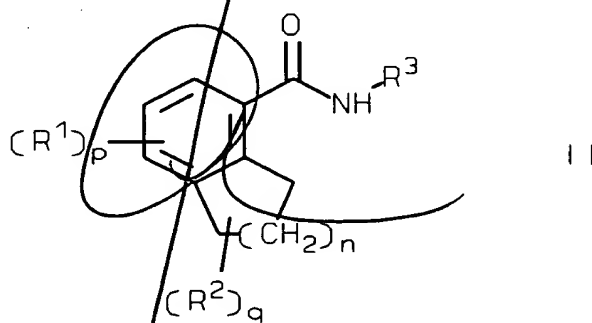
10

in which  $n$ ,  $p$ ,  $q$ ,  $R^1$  and  $R^2$  are as defined above with an alkylating agent of the formula  $R^3L$ , wherein  $R^3$  is defined as above and  $L$  is defined as a leaving group, to form a compound of Formula I.

56. A process according to Claim 55 in which  $R^3$  is a group selected from

20 1-azabicyclo[2.2.2]oct-3-yl;  
1-azabicyclo[2.2.2]oct-4-yl;  
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
25 endo-1-azabicyclo[3.3.1]non-4-yl; and  
exo-1-azabicyclo[3.3.1]non-4-yl.

57. A compound of Formula II:



in which

n is 1, 2 or 3;

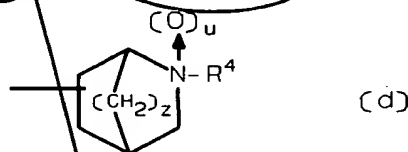
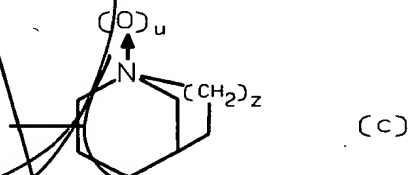
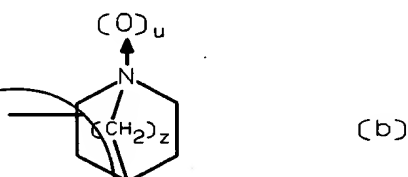
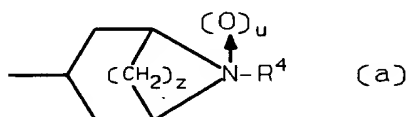
p is 0, 1, 2 or 3;

q is 0, 1 or 2;

5 each  $R^1$  is independently selected from halogen, hydroxy, lower alkoxy, lower alkyl, nitro, amino, amino carbonyl, (lower alkyl)amino, di(lower alkyl)amino, and (lower alkanoyl)amino;

each  $R^2$  is lower alkyl; and

10  $R^3$  is a group selected from Formulae (a), (b), (c) and (d):



in which

u is 0 or 1;

30 z is 1, 2 or 3; and

$R^4$  is  $C_{1-7}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl- $C_{1-2}$  alkyl, or a group  $(CH_2)_t R^5$  where t is 1 or 2 and  $R^5$  is thienyl, pyrrolyl, or furyl, each optionally further substituted by one or two substituents selected from  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from  $C_{1-4}$  alkoxy, trifluoromethyl, halogen,

nitro, carboxy, esterified carboxy, and C<sub>1-4</sub> alkyl optionally substituted by hydroxy, C<sub>1-4</sub> alkoxy, carboxy, esterified carboxy or *in vivo* hydrolyzable acyloxy; the pharmaceutically acceptable salts, individual isomers, 5 or mixtures of isomers thereof.

58. A compound of Claim 57 in which both q and u are 0, p is 0, 1 or 2, each R<sup>1</sup> is independently selected from halogen, lower alkoxy or amino and R<sup>4</sup> is lower 10 alkyl.

59. A compound of Claim 58 in which p is 0, and R<sup>4</sup> is methyl.

60. A compound of Claim 59 in which R<sup>3</sup> is one of the following groups:

1-azabicyclo[2.2.2]oct-3-yl;  
1-azabicyclo[2.2.2]oct-4-yl;  
endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
20 exo-9-methyl-9-azabicyclo[3.3.1]non-3-yl;  
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl;  
endo-1-azabicyclo[3.3.1]non-4-yl; or  
exo-1-azabicyclo[3.3.1]non-4-yl.

25

add  
A<sup>3</sup>